C1 Esterase Inhibitor Subcutaneous (Human) (Haegarda®) New Drug Update

July 2017

Drug Name:	**C1 esterase inhibitor subcutaneous (Human)**
Trade Name (Manufacturer):	**Haegarda (CSL Behring)**
Form:	Subcutaneous injection
Strength:	250 mg
FDA Approval:	June 22, 2017
Market Availability:	Availability as of third quarter, 2017
FDA Approval Classification:	Orphan drug designation
Classification:	To Be Determined (TBD)

DISEASE BACKGROUND[1,2,3]

Hereditary angioedema (HAE) is a rare and life-threatening genetic condition, affecting 1 in 10,000 to 1 in 50,000 people and is characterized by recurrent episodes of angioedema that affects the skin or mucosal tissue of the upper respiratory and gastrointestinal tracts. These attacks are without urticaria or pruritus. Laryngeal involvement occurs and may cause death by asphyxiation. Prior to 2008 and currently available therapies, the mortality rate was approximately 30%.

HAE is caused by a gene defect that controls the C1-inhibitor protein in blood. The ensuing biochemical imbalance causes the production of unwanted peptides that causes capillary leakage into tissue and edema. Typically, first attacks occur in childhood or adolescence and diagnosis is made by the second or third decade of life as attacks increase in frequency during puberty.

Attacks are usually triggered by anxiety, stress, minor trauma, surgery or illnesses like a cold or flu. Other less documented causes of attacks can be physical activities, hormonal changes (as in menstruation or pregnancy) and angiotensin-converting enzyme-inhibitor (ACE-I) therapy.

INDICATION[4]

Haegarda is a plasma-derived concentrate of C1 esterase inhibitor (Human) (C1-INH) indicated for routine prophylaxis to prevent HAE attacks in adolescent and adult patients.

CONTRAINDICATIONS/WARNINGS

C1-INH is contraindicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1-inhibitor preparations or its excipients.

Magellan Rx MANAGEMENT℠

DRUG INTERACTIONS

No interactions studies have been conducted.

COMMON ADVERSE EFFECTS

The most common adverse reactions that occurred in at least 4% of C1-INH patients and occurred more frequently than in control patients were injection site reactions, hypersensitivities, nasopharyngitis, and dizziness.

SPECIAL POPULATIONS

Pregnancy

There are no prospective clinical data available to assess the use of C1-INH during pregnancy, although C1-INH is a normal component of plasma.

Pediatrics

The safety and effectiveness of C1-INH was evaluated in a subset of 6 patients aged 12 to under 17 years old in the approval study. The outcomes of the subgroup were consistent with overall study results.

Geriatrics

The safety and effectiveness of C1-INH was evaluated in a subset of 8 patients aged 65 to 72 years old in the approval study. The outcomes of the subgroup were consistent with overall study results.

Hepatic/Renal Impairment

Pharmacokinetic studies have not been conducted to evaluate C1-INH in specific patient populations in regards to the presence of hepatic or renal impairment.

DOSAGES

The recommended dosage of C1-INH is 60 international units (IU)/kg via subcutaneous (SC) injection twice weekly (every 3 to 4 days). C1-INH is provided as a kit with a vial of freeze-dried powder for reconstitution and a vial of sterile water for injection. The preservative-free solution should be used within 8 hours of reconstitution.

Haegarda can be self-administered. The patient or caregiver should be trained on how to administer C1-INH.

CLINICAL TRIALS[5]

A literature search was conducted using "subcutaneous c1 esterase inhibitor" AND "hereditary angioedema".

COMPACT trial: The safety and efficacy of C1-INH, a nanofiltered, plasma derived, C1 inhibitor preparation was established with the FDA in a phase 3, double-blind, randomized, placebo-controlled,

32-week, cross over study in 90 patients with a diagnosis of type I or type II HAE. Patients were to have had 4 or more attacks in a consecutive 2-month period within 3 months before study screening.

Patients were randomly assigned to 1 of 4 treatment groups, with each involving two 16-week treatment periods. Patients received either 40 IU or 60 IU per kg of C1-INH self-administered SC twice weekly followed by placebo, or vice versa. The primary efficacy endpoint was the number of angioedema attacks. The secondary efficacy endpoint were the proportion of patients who had a response and the number of times a rescue medication was used. A response was defined as a ≥ 50% reduction in the number of attacks while on C1-INH as compared with placebo.

Of the 90 patients randomized to groups, 79 completed the study. Both doses of C1-INH, compared to placebo, reduced the incidence of attacks. The 40 IU group experienced 2.42 less attacks per month compared to placebo with a response rate of 76% and the 60 IU group experienced 3.51 lesser attacks per month when compared to placebo with a 90% response rate. Rescue medication need was also reduced when compared to placebo. The 40 IU group only required rescue medication of 1.13 uses per month compared to placebo's 5.55 uses per month. The 60 IU group only required 0.32 uses of rescue medication compared to placebo's 3.89 uses. The severity of attacks in the treatment arms were also less severe. Adverse events were mild and similar across all study groups.

OTHER DRUGS USED FOR CONDITION[6]

There are several medications on the U.S. market for HAE. There are 2 types of C1-INH type medications. Plasma derived C1-INH products include Cinryze® and Berinert®. Human recombinant C1-INH includes Ruconest®. There is also the kallikrein inhibitor, ecallantide (Kalbitor®) in the U.S. and the bradykinin B2-receptor antagonist, icatibant (Firazyr®). Older and sometimes less studied agents used for treatment HAE include fresh frozen plasma (FFP), tranexamic acid, aminocaproic acid, and androgens. Of note, HAE related angioedema does not respond well to antihistamines, epinephrine, and glucocorticoids.

PLACE IN THERAPY[7,8]

The therapeutic approach to HAE consists of optimizing management of acute attacks with on-demand therapy and then prophylaxis or prevention of attacks. Berinert, Kalbitor, Firazyr and Ruconest are all approved for treatment of acute attacks. Firazyr and Kalbitor are the only acute attack products given via SC injection.

Cinryze was the only FDA-approved C1-INH product, prior to Haegarda, for preventing HAE attacks but is only available as an IV formulation. It can be given as a home infusion, twice weekly.

Prophylaxis can be given as short-term, generally prior to surgery or certain medical or dental procedures. In the past, androgens or tranexamic acid have been used but with limited efficacy and many side effects. The U.S. Hereditary Angioedema Association (HAEA) recommends that C1-INH or empiric fresh frozen plasma prior to surgery be given to avoid induction of an attack. Although not FDA-approved in pediatrics, Berinert has been used in certain situations, pre-operatively, when larger doses would be detrimental in smaller children off-label. Patients being evaluated for long-term prophylaxis should take into account attack frequency, severity, comorbid conditions, access to emergent care, patient experience with therapy, and preference.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Hereditary Angioedema

Clinical Edit	**INITIAL**
	• Must be prescribed by, or in consultation with, a specialist in: allergy, immunology, hematology, pulmonology, or medical genetics; **AND**
	• Patient must be at least 12 years of age; **AND**
	• Patient has a history of 1 of the following criteria for long-term HAE prophylaxis:
	  ○ History of 2 or more severe HAE attacks per month (e.g., airway swelling, debilitating cutaneous or gastrointestinal episodes); **OR**
	  ○ Patient is disabled more than 5 days per month by HAE; **OR**
	  ○ History of recurrent laryngeal attacks caused by HAE; **AND**
	• Treatment of patient with "on-demand" therapy (e.g., Kalbitor, Firazyr, Ruconest, or Berinert) did not provide satisfactory control or access to "on-demand therapy" is limited; **AND**
	• Patient has tried and failed, is intolerant to, or has a contraindication to attenuated (17 alpha-alkylated) androgens (e.g., danazol) for HAE prophylaxis; **AND**
	• Confirmation that the patient is avoiding the following possible triggers for HAE attacks:
	  ○ *Helicobacter pylori* infections (confirmed by lab test); **AND**
	  ○ Estrogen-containing oral contraceptive agents OR hormone replacement therapy; **AND**
	  ○ Antihypertensive agents containing angiotensin-converting enzyme (ACE) inhibitors; **AND**
	• Patient has one of the following clinical presentations consistent with HAE subtype:
	  ○ HAE-I; **OR**
	  ○ HAE-II; **OR**
	  ○ HAE-III.
	
	RENEWAL
	• Patient continues to meet initial criteria; **AND**
	• Significant improvement in severity and duration of attacks have been achieved and sustained; **AND**
	• Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe hypersensitivity reactions, thromboembolic events, etc.

Quantity Limit	• Haegarda 2,000 IU SDV kit: 16 kits per 28 days • Haegarda 3,000 IU SDV kit: 8 kits per 28 days
Duration of Approval	12 months

REFERENCES

1 Cicardi M, Zuraw B. Hereditary angioedema: epidemiology, clinical manifestations, exacerbating factors and prognosis. In: UpToDate, Feldweg AM (Ed), UpToDate, Waltham, MA. Accessed on July 03, 2017.
2 CSL Behring Press Release. Available at: https://www.multivu.com/players/English/8122051-csl-behring-haegarda-fda-approval/. Accessed July 3, 2017.
3 Available at: http://www.haea.org/what-is-hae/hae-the-disease/. Accessed July 3, 2017.
4 Haegarda [prescribing information]. Kankakee, IL. CSL Behring. July 2017.
5 Haegarda [prescribing information]. Kankakee, IL. CSL Behring. July 2017.
6 Cicardi M, Zuraw B. Hereditary angioedema: treatment of acute attacks. In: UpToDate, Feldweg AM (Ed), UpToDate, Waltham, MA. Accessed on July 03, 2017.
7 Cicardi M, Zuraw B. Hereditary angioedema: general Care and Long-Term Prophylaxis. In: UpToDate, Feldweg AM (Ed), UpToDate, Waltham, MA. Accessed on July 03, 2017.
8 Available at: http://www.haea.org/what-is-hae/hae-the-disease/. Accessed July 3, 2017.